

Essential Tremor: Genetics Working Group

Session 5 Document

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I. What do we know?

Previous studies suggest there is a genetic contribution to essential tremor (ET). Researchers initially utilized large pedigrees to detect chromosomal regions harboring genes having a large effect on ET risk. Despite the identification of extended pedigrees segregating what appeared to be an autosomal dominant form of ET, results have been inconsistent. Traditional linkage approaches implicated 3 chromosomal regions (ET1, ET2, and ET3), but the genes nominated within these regions have not been definitely shown to affect disease risk. More recently, analysis of whole exome sequencing reported two genes, again in large extended pedigrees, but results have continued to be inconsistent. To complement these efforts to identify rare variants with large effect on disease risk, genomewide association studies (GWAS) have been performed to detect common variants with presumably small to moderate effect on disease risk. These modestly powered case-control studies have nominated single nucleotide polymorphisms (SNPs); however, replication has been inconsistent.

II. What do we need to know?

Gene discovery in ET appears to be in a similar position to that of other disorders a few years ago. If we consider the lessons learned from these other disorders, it appears that several key elements should be considered to successfully move ET genetics forward.

First, it is important to consider the full allelic spectrum of variants that could affect risk. This would require studies designed to detect rare variants as well as common variants. Second, sample size is critical in all gene discovery efforts. Studies to date have focused on very large ET families or have utilized modest numbers of ET cases and controls. It is necessary to greatly expand the number and types of ET subjects included in genetic analysis. In particular, multiplex families of differing size along with sporadic ET should be analyzed. Third, a range of ET-relevant phenotypes should be collected in all study subjects to allow genetics to inform phenotyping. Specifically, heritability can be used to identify optimal phenotypes for genetic analysis.

III. How can we get there?

We have three primary recommendations that could accelerate the trajectory of ET genetic discovery.

- Implementation of brief assessment instruments that facilitates uniform phenotyping of all ET subjects and collects data on a range of ET-relevant or potentially relevant characteristics
- Creation of a biorepository of ET samples that are linked to uniform phenotypic data and family history/ pedigrees
- Broad data and sample sharing to ensure that fully powered studies can be proposed and completed

Overall: Genetics is a valid, important approach to understanding tremor etiology. Efforts to identify important genetic effects do not need to wait on fully completed, clinical definitions agreed upon by the research community. Rather, we can be immediately productive, particularly in large scale collaborative designs.